REMARKS

Claims 160-200 are pending. Claims 1-159 and 164 have been canceled and claims 167-200 have been withdrawn as directed to a non-elected species. Claims 160-163 and 165-166 stand rejected. Claim 160 is amended to include a recitation that the insertion compound reacts with an amide group and prevents recrystallization of said denatured segment.

Support for the amendment is found in the specification in paragraphs **[0005]**, **[0006]**, **[0022]**, **[0030]** and elsewhere in the specification. No new matter is added.

Item 1

Applicant notes that the reference cited in the December 7, 2006, Information Disclosure Statement has been considered.

Item 3

The Applicant respectfully acknowledges that the rejection of claims 160-163 under 35 U.S.C. 102(b) as anticipated by Adams et al. (U.S. Patent No. 5, 641,658) has been withdrawn.

Item 4. Rejections under 35 U.S.C. §102(e)

Claims 160-163 and 165 stand rejected as anticipated by Heller et al. (U.S. Patent No. 6,017,696). Office Action at page 2.

> The Office Action (p. 2) asserts that Heller teaches an array of microscopic locations:
> Thus, the first and most important aspect of the present invention is a device with an array of electronically programmable and self-addressable microscopic locations. Each microscopic location contains an underlying working direct current (DC) micro-electrode supported by a substrate. The surface of each micro-location has a permeation layer for the free transport of small counter-ions, and an attachment layer for the covalent coupling of specific binding entities. hese unique design features provide the following critical properties for the device: (1) allow a controllable functioning DC electrode to be maintained beneath the microlocation; (2) allow electrophoretic transport to be maintained; and (3) separate the affinity or binding reactions from the electrochemical

and the adverse electrolysis reactions occurring at the electrode (metal) interfaces. It should be emphasized that the primary function of the micro-electrodes used in these devices is to provide electrophoretic propulsion of binding and reactant entities to specific locations.

By "array" or "matrix" is meant an arrangement of addressable locations on the device. The locations can be arranged in two dimensional arrays, three dimensional arrays, or other matrix formats. The number of locations can range from several to at least hundreds of thousands. Each location represents a totally independent reaction site.

Col. 7, ll. 6-31.

The Office Action (p. 3) further asserts that Heller also teaches chips having nucleic acids located in multiple micro locations:

In cases of hybridization analysis with very low target sequence copy number (e.g., HIV, septic blood infections, etc.), the multiplication or amplification of target DNA sequence would enable sensitivity to be improved by amplification of purified target DNA and/or RNA directly on an APEX device. Amplification would also reduce the requirement for very high yield preparative steps prior to hybridization analysis.

APEX amplification protocol provides complete electronic control of DNA movements, denaturation, and synthesis reactions. Most importantly DNA hybrids are denatured electronically without the use of high temperature or the need for thermophilic polymerases or other thermal stable enzymes.

As a first example, DNA synthesis can be achieved with high fidelity using DNA polymerase (Klenow large fragment) and without the need for thermal cycling. In this example, one DNA strand is amplified in a way that leaves it covalently bound to a micro-location. The procedure is carried out in the following manner: 1) the known target sequence is electronically hybridized to a capture probe of known sequence on an addressed micro-location, 2) synthesis of nascent complementary strand DNA (-) by DNA polymerase primed by the capture probe is carried out, 3) the newly synthesized DNA hybrids are electronically denatured, 4) annealing of target strand DNA to non-elongated capture probe and annealing of - strand complementary probe to nascent - strand DNA is carried out, 5) the synthesis of nascent target strand DNA(+) by DNA polymerase and concomitant synthesis of - strand DNA as in 2 is carried out, thereby

> doubling the number of + and - strands each time these steps are repeated, and 6) size selection of amplified target is carried out by hybridization to a specially designed complimentary probe.

Col. 46, ll. 11-44.

The Office Action (p. 3) continues, suggesting that Heller further teaches providing at least one double stranded nucleic acid molecule:

> As a first example, DNA synthesis can be achieved with high fidelity using DNA polymerase (Klenow large fragment) and without the need for thermal cycling. In this example, one DNA strand is amplified in a way that leaves it covalently bound to a micro-location. The procedure is carried out in the following manner: 1) the known target sequence is electronically hybridized to a capture probe of known sequence on an addressed micro-location, 2) synthesis of nascent complementary strand DNA (-) by DNA polymerase primed by the capture probe is carried out, 3) the newly synthesized DNA hybrids are electronically denatured, 4) annealing of target strand DNA to non-elongated capture probe and annealing of - strand complementary probe to nascent - strand DNA is carried out, 5) the synthesis of nascent target strand DNA(+) by DNA polymerase and concomitant synthesis of - strand DNA as in 2 is carried out, thereby doubling the number of + and - strands each time these steps are repeated, and 6) size selection of amplified target is carried out by hybridization to a specially designed complimentary probe.

Col. 46, ll. 25-44.

The Office Action (p. 3) notes that Heller teaches denaturing at least one of the strands, as follows:

> Polarity at micro-location 1 is reversed and voltage is applied to separate the two strands. The amount of voltage and the time period of application will be dependent on the length and base composition of the hybrid DNA complex. These parameters may be determined empirically or calculated from electronic denaturation curves.

Col. 46, l. 63 to Col. 47, l. 3.

Finally with regard to claim 160, the Office Action (p. 3) contends that Heller also teaches attaching at least one insertion compound to at least one nucleotide:

> DNA polymerase and dNTP's are electrophoretically transported to micro-location 1. The capture probe provides a 3' end for DNA polymerase and the captured target sequence provides the template. Current sufficient to maintain a concentration of reagents amenable to synthesis are applied. The current may be constant or pulsed. These parameters can be manipulated to obtain differing ranges of lengths of nascent complementary (-) strand.

Col. 46, ll. 55-62, and

> Oligos need to be annealed to both + and - DNA strands to provide primer sites for DNA polymerase. For the target or + strand this is accomplished by electrophoretic transport of + strand to un-elongated capture probe. This will occur as long as un-elongated capture probe is in excess to elongated, covalently bound - strand DNA. Complementary probe is electrophoresed to the micro-location and binds to covalently bound - strand DNA. Now both + and - strands have primer bound to them and are templates DNA polymerase catalyzed synthesis (see figure). Binding of complementary probe may also occur with noncovalently bound - strand DNA, however these hybrids will not be electronically denatured and therefore should have little impact on the overall amplification.
>
> Step 5) Synthesis of Two New Strands of DNA
>
> Step 2 is repeated and since both + and - strands are primed templates, the amount of sequence specific DNA doubles. This geometric increase in the amount of DNA will occur each time these steps are repeated.
>
> Step 6) Size Selection of Amplified Target Sequence
>
> The nucleotide sequence of the complementary probe will determine the size and sequence of the amplified target DNA. Therefore, the amplified DNA can be custom designed to enhance efficiency in subsequent analysis and/or manipulation.
>
> Other enzymes can be used in the amplification method of this invention, including, but not limited to, other DNA polymerases, T7 or SP6 RNA polymerases, reverse transcriptases, DNA ligases, and polynucleotide phosphorylases, and combinations of other nucleic acid modifying enzymes (endonucleases, exonucleases, etc.).

Col. 47, ll. 4-35.

Unlike the disclosure of Heller et al., claim 160 as amended incorporates the recitation that the insertion compound prohibits recrystallization of the denatured segment. The specification states that the "chemical moiety, or insertion compound ... prohibits recrystallization of the at least one denatured portion to which the chemical moiety is attached." Paragraph 0022.

Moreover, "[a]t least one chemical moiety that prohibits recrystallization of the at least one denatured portion of the at least one, [sic] DNA molecule is attached to at least one nucleotide in the at least one denatured portion of the at least one DNA molecule." Paragraph 0005.

Furthermore, the claim, as amended, includes a limitation to the reaction of the insertion compound "with an amide group." The specification that the insertion compound "can react with amide groups of the bases, to inhibit them from recrystallizing or renaturing." See paragraph [0030].

In contrast to the invention claimed in amended claim 160, Heller et al. does not teach inhibition of recrystallization by an insertion compound as taught and claimed by the instant invention. Heller et al. is not directed to prevention of recrystallization. Moreover, Heller does not teach that an insertion group can react with an amide to inhibit recrystallization.

Importantly, Heller et al. teaches away from use of an insertion compound at all. "The ability to provide electronic stability control to hybridizations also provides new mechanisms for detecting DNA hybridization without using a reporter group labeled DNA probe." Col. 23, line 65 to Col. 24, line 1. (Emphasis added). Heller emphasizes that not using a detector group is an important aspect of the invention: "The following reiterates *important advantages* the devices of this invention provide for nucleic acid hybridization reactions and analysis: ... (15) The development of a detection method which *eliminates* the need for using covalently labeled

reporter probes or target DNA to detect hybridization." Col. 24, ll. 19-67. (Emphasis added.) By thus *eliminating* the need for covalent attachment of an insertion compound, Heller cannot be reasonably construed to teach covalent labeling.

For at least the above reasons, claim 160 and claims that depend from claim 160 are not anticipated by Heller et al.

Items 5-6. Rejection under 35 U.S.C. §103 over Heller et al.

Claim 166 is rejected as obvious over Heller et al. Office Action page 4. The Office Action states that Heller "does not specifically teach the use of 100 nanosecond pulses." Office Action page 6. However, Heller teaches "the amount of voltage and the time period of application will be dependent on the length and base composition of the hybrid DNA complex (see column 46, line 66 to column 47, line 1)." *Id.* According to the Office Action one of ordinary skill in the art would routinely optimize the time for application of current.

Claim 166 depends from claim 160 as amended and incorporates all the recitations thereof. For the reasons presented above, Heller et al. does not disclose or render obvious all the elements of claim 160 as amended. For at least this reason, the rejection of claim 166 as obvious over Heller should be withdrawn.

Withdrawal of all rejections is respectfully requested.

Claims 167-200 will be amended to conform to claims 160-166 upon allowance of claims.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

A Request for Continuing Examination is filed herewith. Please charge the fee for the RCE to our Deposit Account No. 50-0510 under Order No. YO009220US4. Applicants believe no additional fees are due with this amendment. However, if any additional fees are due, please charge our Deposit Account No. 50-0510, under Order No. YO998229US4 from which the undersigned is authorized to draw.

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Respectfully submitted,

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